UNC SCHOOL OF MEDICINE

Increased Nuchal Translucency vs. Cystic Hygroma

Definitions:

For consistency, we propose reporting the nuchal translucency measurement, not as percentile or MoM by CRL.

Nuchal Translucency: Nuchal translucency (NT) is the sonographic appearance of a collection of fluid under the skin behind the fetal neck in the first trimester. The NT measurements are most informative when the CRL is between 45 and 84 mm[10]. NT<3.0 mm is considered normal, regardless of specific CRL.

--Nuchal translucency cannot be adequately assessed if there is:

>Unfavorable fetal lie

>Unfavorable gestational age (<45 mm or >84 mm)

Increased Nuchal Translucency: A increased nuchal translucency is defined as an NT≥3.0 mm when CRL is ≥45 mm and is confined to the fetal neck. For consistency, please use the nuchal translucency measurement, not percentiles by CRL.

--the lucent region is not septated

Cystic Hygroma: Cystic hygromas are congenital malformations of the lymphatic system, characterized by fluid filled lesions at sites of lymphatic–venous connections along the posterior neck **and** back, and in which septations may develop.[10,14]

--Most commonly diagnosed when CRL ≥45 mm

--May or may not be septated

--Distinguished from thick NT by extension down fetal back and/or septations

Implications of Nuchal Translucency Size

NT measurement	Chromosomal defect (karyotypically visible)	Microarray (subkarotypic)	Single-gene (Noonan or other)	Fetal death	Major fetal anomaly	Alive and well
3.0-3.4 mm	3.7%-20% [11]	2-5%[2,9]	>0.5%[1]	1.3% [11]	2-20%[2]	93% [11]
3.5-4.4mm	21% [11]	4-7%[4,12,15]		2.7%[11]	2-20%[2]	70-90%[11]
4.5-5.4mm	33% [11]			3.4%[11]	18%[11]	50-80%[11]
5.5-6.4mm	50% [11]			10%[11]	24%[11]	30-45%[11]
>6.5mm	64% [11]			19%[11]	46%[11]	15%[11]
Cystic hygroma (size irrelevant)	50%[8]	10-15%	3-5%	25%[13]	33%[13]	17%[7]

Additional Statistics[19]:

Noonan syndrome and other *RAS*-opathies:

NT>3.5mm has a 1% risk

NT>5mm has a 15% risk

Non-isolated NT has a 14% risk

Exome sequencing:

Yield of exome is 3.7% with an isolated NT>3.5mm

Yield of exome is 24-32% if multiple anomalies are present

Take-away: The clinical management follows a similar approach regardless of the variations of appearance when NT≥3.5mm or cystic hygroma are diagnosed.

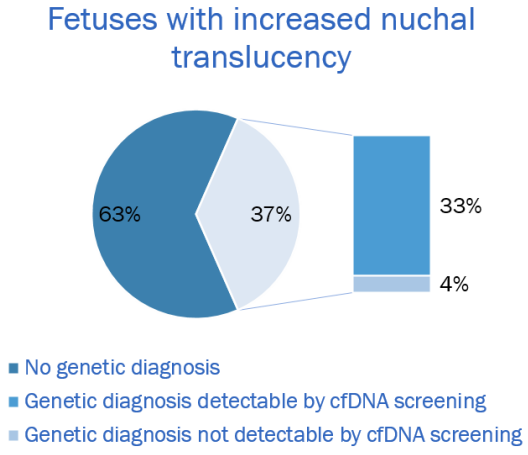
Cystic Hygroma Risk Reduction Based on Genetic Testing and Ultrasound

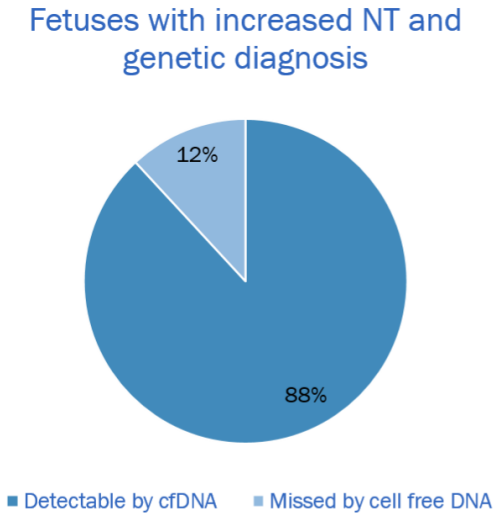
If karyotype is normal, there is a 50% risk of a structural malformation (specifically 25% of remaining fetuses have a cardiac defect). If a euploid pregnancy has a normal anatomy ultrasound, there is a 95% chance for normal short term pediatric outcomes.[8,13]

Increased NT/Cystic Hygroma and Cell-Free DNA Screening

Increased Nuchal Translucency

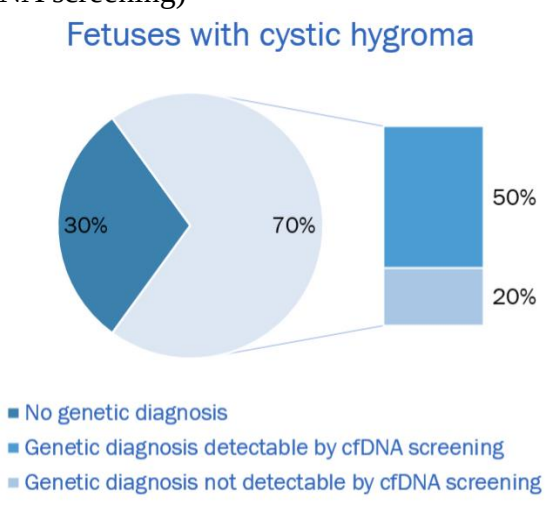
4-7%* of all increased nuchal translucencies have a genetic etiology that would be missed by cell-free DNA screening. (12-19% of thick NTs with a genetic etiology have a diagnosis that is standardly undetectable by cell-free DNA screening)[7]

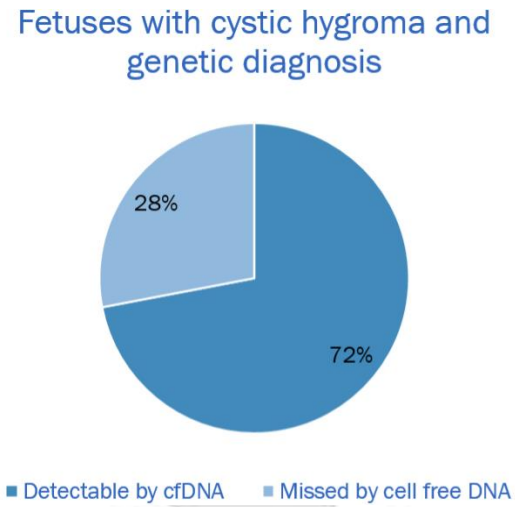




Cystic Hygroma

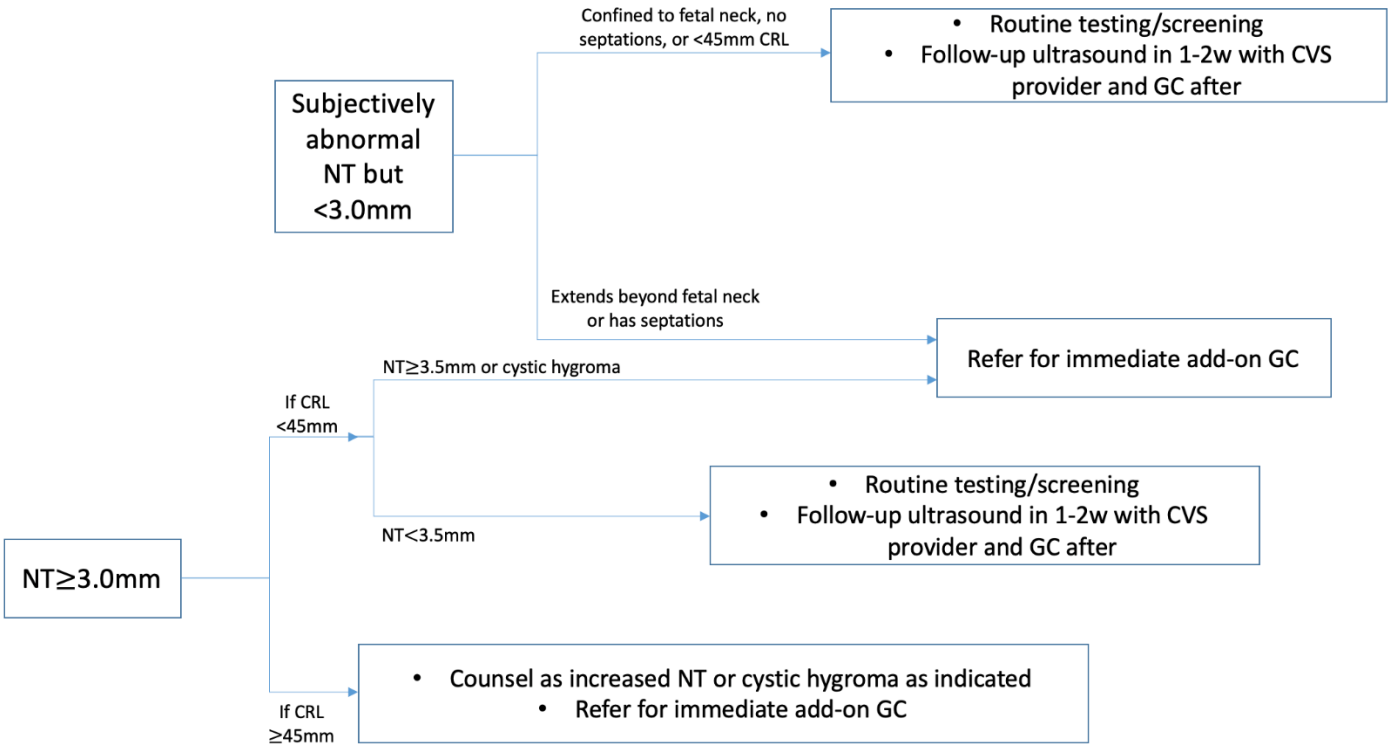
20%* of all hygromas have a genetic etiology that would be missed by cell-free DNA screening. (Approximately 28% of hygromas with a genetic etiology have a diagnosis that is standardly undetectable by cell-free DNA screening)





*this assumes 100% detection rate of aneuploidy by cell-free DNA screening; in reality, this is an underestimate. Depending on the condition, detection rates by cell-free DNA screening ranges from 90-99%.

Proposed Procedure



Follow-up Ultrasound Recommendations:

- Consider repeat ultrasound with a CVS provider at **<14w**
- **16w US**: can detect 41% of associated structural anomalies[18]
    - With a normal 16w scan and normal diagnostic testing, there is an 85% risk of favorable outcome
- **19-20w US** detailed anatomy ultrasound
- Fetal ECHO

Typical Genetic Testing Options:

Non-invasive (blood):

-Cell-free DNA screening for common aneuploidy (lab-specific if concern for triploidy)
-NIPS for single gene disorders Lab Info & Condition List

CVS/Amniocentesis:

-FISH for common aneuploidy (21, 18, 13, X/Y)
-Karyotype and/or microarray
-*RAS*-opathy panel vs other specific feature panel (ex. Skeletal dyaplasias) vs Exome
    - Specifically consider if NT≥3.5mm or if multiple anomalies
-Fetal infection, if indicated
-Option to save cells for future testing based on additional ultrasounds.

Common Considerations:

Should we be assessing the NT if the CRL is <45mm?

No. We do not routinely attempt to measure the NT prior to a CRL of ≥45mm. However, a subjectively abnormal NT may be noticed during routine midsagittal views which subsequently leads to more detailed measurements.

Increased NT or cystic hygroma noted when CRL is <45 mm

See definitions above.

- Studies have demonstrated lower rates of chromosomal abnormalities and a higher proportion of normal birth outcomes when nuchal translucency thickness is detected in fetuses with CRL measuring < 45 mm.[8]
- Due to lack delineation of implications of an increased NT for a CRL <45 mm, the protocol is to:
    - Repeat ultrasound in 2-3 weeks with GC scheduled immediately following.
    - Request to have the follow-up scan scheduled with a provider who performs CVS
    - Consider/discuss routine aneuploidy screening

However, if there is a distinct cystic hygroma or NT≥3.5mm:

- Counsel as such and refer for genetic counseling immediately (as an add-on same day).

Subjectively large or abnormal-appearing NT measurement that is <3.0 mm

- If the lucent region is septated or extends down the fetal back, counsel as a cystic hygroma and refer for genetic counseling immediately (as an add-on same day)
- If this region cannot be diagnosed as a cystic hygroma at this time, routine aneuploidy screening can be considered, and offer a follow-up ultrasound in 1-2 weeks.

Resources:

1. Ali MM, Chasen ST, Norton ME. Testing for Noonan syndrome after increased nuchal translucency. Prenat Diagn. 2017 Aug;37(8):750-753. doi: 10.1002/pd.5076. Epub 2017 Jun 28. PMID: 28569377.

2. Bardi, F, Bosschieter, PFN, Verheij, JBGM, et al. Is there still a role for nuchal translucency measurement in the changing paradigm of first trimester screening?. Prenatal Diagnosis. 2020; 40: 197– 205. https://doi-org.libproxy.lib.unc.edu/10.1002/pd.5590

3. Chung JH, et al., The distribution of fetal nuchal translucency thickness in normal Korean fetuses. J Korean Med Sci. 2004 Feb;19(1):32-6.PMID: 14966338

4. Grande M, Jansen FA, Blumenfeld YJ, Fisher A, Odibo AO, Haak MC, Borrell A. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015 Dec;46(6):650-8. doi: 10.1002/uog.14880. PMID: 25900824.

5. Hadlock FP et. al.,Fetal crown-rump length: reevaluation of relation to menstrual age (5-18 weeks) with high-resolution real-time US. Radiology. 1992 Feb;182(2):501-5.PMID: 1732970.

6. Lugthart, M. A., Bet, B. B., Elsman, F., Kamp, K., Bakker, B. S., Linskens, I. H., Maarle, M. C., Leeuwen, E., & Pajkrt, E. (2021). Increased nuchal translucency before 11 weeks of gestation: Reason for referral? Prenatal Diagnosis. https://doi.org/10.1002/pd.6054

7. Miranda J, Paz Y Miño F, Borobio V, Badenas C, Rodriguez-Revenga L, Pauta M, Borrell A. Should cell-free DNA testing be used in pregnancy with increased fetal nuchal translucency? Ultrasound Obstet Gynecol. 2020 May;55(5):645-651. doi: 10.1002/uog.20397. Epub 2020 Apr 7. PMID: 31301176.

8. Malone, F. , Ball, R. , Nyberg, D. , Comstock, C. , Saade, G. , Berkowitz, R. , Gross, S. , Dugoff, L. , Craigo, S. , Timor-Tritsch, I. , Carr, S. , Wolfe, H. , Dukes, K. , Canick, J. , Bianchi, D. & D'Alton, M. (2005). First-Trimester Septated Cystic Hygroma. Obstetrics & Gynecology, 106 (2), 288-294. doi: 10.1097/01.AOG.0000173318.54978.1f.

9. Petersen OB, Smith E, Van Opstal D, et al. Nuchal translucency of 3.0-3.4 mm an indication for NIPT or microarray? Cohort analysis and literature review. *Acta Obstet Gynecol scand.* 2020;99:765-774. https://doi.org/10.1111/aogs.13877

10. Scholl, J., and Chasen, S. T. (2016) First trimester cystic hygroma: does early detection matter?. *Prenat Diagn*, 36: 432– 436. doi: 10.1002/pd.4799.

11. Souka, A. P., von Kaisenberg, C. S., Hyett, J. A., Sonek, J. D., & Nicolaides, K. H. (2005). Increased nuchal translucency with normal karyotype. American Journal of Obstetrics and Gynecology, 192(4), 1005–1021. https://doi.org/10.1016/j.ajog.2004.12.093

12. Su L, Huang H, An G, et al. Clinical application of chromosomal microarray analysis in fetuses with increased nuchal translucency and normal karyotype. *Mol Genet Genomic Med*. 2019;7(8):e811. doi:10.1002/mgg3.811

13. Tayyar, A., Tayyar, A., & Tayyar, M. (2017). Prenatal management of cystic hygroma and long term outcomes. Medicine Science | International Medical Journal, 1. https://doi.org/10.5455/medscience.2016.05.8551

14. Yakıştıran, B., Altınboğa, O., Canpolat, E., Çakar, E. Ş., Çelen, Ş., Ali Turhan Çağlar, & Üstün, Y. E. (2020). Analysis of cystic hygroma diagnosed in the first trimester: Single-center experience. *Journal of the Turkish German Gynecological Association, 21*(2), 107-110. doi:http://dx.doi.org.libproxy.lib.unc.edu/10.4274/jtgga.galenos.2019.2019.0032

15. Xue S, Yan H, Chen J, Li N, Wang J, Liu Y, Zhang H, Li S, Zhang W, Chen D, Chen M: Genetic Examination for Fetuses with Increased Fetal Nuchal Translucency by Genomic Technology. Cytogenet Genome Res 2020;160:57-62. doi: 10.1159/000506095

16. Yakıştıran, B., Altınboğa, O., Canpolat, E., Çakar, E. Ş., Çelen, Ş., Ali Turhan Çağlar, & Üstün, Y. E. (2020). Analysis of cystic hygroma diagnosed in the first trimester: Single-center experience. Journal of the Turkish German Gynecological Association, 21(2), 107-110. doi:http://dx.doi.org.libproxy.lib.unc.edu/10.4274/jtgga.galenos.2019.2019.0032

17. Zhao XR, Gao L, Wu Y, Wang YL. Application of chromosomal microarray in fetuses with increased nuchal translucency. J Matern Fetal Neonatal Med. 2020 May;33(10):1749-1754. doi: 10.1080/14767058.2019.1569622. Epub 2019 Jan 27. PMID: 30688128.

18. Le Lous M, et al. The performance of an intermediate 16th-week ultrasound scan for the follow-up of euploid fetuses with increased nuchal translucency. Prenat Diagn. 2016;36(2): 148-53.

19. Kelley, J, McGillivray, G, Meagher, S, Hui, L, Increased nuchal translucency after low-risk noninvasive prenatal testing; what should we tell prospective parents? Prenat Diagn. 2021; 41(10):1305-1315. doi:10.1002/pd.6024

20. Malone CM, Mullers S, Kelliher N, Dalrymple J, O'Beirnes J, Flood K, Malone F. Euploid First-Trimester Cystic Hygroma: A More Benign Entity than Previously Thought? Fetal Diagn Ther. 2021;48(9):667-671. doi: 10.1159/000519056. Epub 2021 Sep 21. PMID: 34569548.

These algorithms are designed to assist the primary care provider in the clinical management of a variety of problems that occur during pregnancy. They should not be interpreted as a standard of care, but instead represent guidelines for management. Variation in practices should take into account such factors as characteristics of the individual patient, health resources, and regional experience with diagnostic and therapeutic modalities.

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